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(21) International Application Number: PCT/AU96/00642 (22) International Filing Date: 14 October 1996 (14.10.96) (30) Priority Data: PN 5965 13 October 1995 (13.10.95) AU (71)(72) Applicant and Inventor: PRISCOTT, Paul, Kenneth [AU/AU]; 32 Nichols Avenue, Revesby, NSW 2212 (AU). (74) Agent: H.R. HODGKINSON & CO.; Level 3, 20 Alfred Street, Milsons Point, NSW 2061 (AU).		(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KP, KR, LK, LR, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>With amended claims and statement.</i>
(54) Title: BIOMATERIALS FOR USE IN MEDICAL APPLICATIONS (57) Abstract A biomaterial such as a synthetic polymer, metal or ceramic therapeutically effective amount of Triclosan (2,4,4'-trichloro-2'-hydroxy diphenyl ether) used in the manufacture of medical devices or prostheses for internal or in vivo medical applications. Medical devices or prostheses containing such biomaterials are also disclosed, including prosthetic hip and knee joints, artificial heart valves, voice and auditory prostheses.		

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BIOMATERIALS FOR USE IN MEDICAL APPLICATIONS

TECHNICAL FIELD

The present invention relates to improvements in biomaterials including ceramics and polymeric materials for use in medical applications, particularly in the use of such polymeric materials in the manufacture of medical devices and prostheses. The present invention also relates to the medical devices and prostheses per se comprising such biomaterials.

BACKGROUND ART

Hospital infection is not a new phenomenon. It has long been recognised as a hazard of hospitalisation connected with, for example, surgical wards. Historically, its incidence was mitigated by using disinfectants and by building hospitals according to the dilution principle, i.e. with adequate ventilation. However, the effectiveness of the dilution principle has been reduced by, for example, the tendency towards vertical or multiple story high-rise buildings and lowered ceilings, and by the concentration - for good economic and clinical reasons - of the chronic sick. More importantly, the blanket use of antibiotics over the past 50 years has led to the selective accumulation of insensitive bacterial populations.

Individuals seek medical or allied health professional help usually as consequence of developing impaired personal health. Advances in medicine have been dramatic during the last 50 years and as a result significantly more medical conditions are able to be successfully treated than was previously possible. One of the consequences of these advances is the much greater application of invasive procedures and the use of medical devices and prostheses in treatment regimens. Attendant with this is the parallel increase in the infection rates in patients where the invasive procedures have been used. These are referred to as iatrogenic infections (i.e. brought about by the medical procedure). The likelihood of developing an iatrogenic infection is further increased by other risk factors such as impaired patient immuno-competency, length to time of device residency, surgical/nursing hygiene practices, etc.

The biomaterials used in the manufacture of implanted prosthetic devices profoundly impair the ability of the host to opsonise and phagocytose invading microbes. As a result, while these devices generally provide effective relief from painful, crippling and life-threatening disorders, they can also induce vulnerability to infection in the recipients. The surfaces of the implants are susceptible to colonisation by microbial biofilms. The cells in the biofilms are further protected against opsonophagocytosis and are also resistant to antibacterials. Device associated infections thus tend to be refractile to antibiotic therapy and in many cases the device has to be removed before the infection will respond to treatment. Infection rates per implantation operation in totally implanted devices, such as, artificial hips and knees, have fallen over the years. However, devices that are partly implanted into body cavities or pass transcutaneously into tissues are particularly susceptible to infection. For example, infection rates of 2.3-4.5% have been reported for central line vascular catheters. The incidence of infection is related to the length of time the device is in place. Infection rates for urethral catheters indwelling for more than 28 days approach 100%.

While several ingenious approaches are currently being taken to modify the surfaces of biomaterials, until now it has not yet proved possible to reduce the deleterious affects on the host or frustrate the surface colonisation mechanisms that microbes have evolved as a basic survival strategy in natural aquatic habitats.

The prosthetic devices available to modern medicine provide effective relief from a range of painful, crippling and life-threatening disorders. Some, such as, artificial heart valves and haemodialysis shunts, have become essential for the survival of many patients, others, such as, prosthetic joints, enable patients to regain the ability to perform important physical activities. Artificial devices have been successfully developed and incorporated into nearly all of the body systems and the numbers of patients receiving implants continues to increase. There is no doubt that prostheses have both prolonged and improved the quality of life for millions of individuals.

In the wake of this progress has come the problem of device associated infection, which now accounts for a substantial proportion of the infections acquired in hospitals and other health care facilities. Unfortunately, the biomaterials used in the manufacture of the devices, synthetic polymers, metals and ceramics are vulnerable to colonisation by microorganisms. Contamination can occur during the implantation of the device or later on during its working life and the resulting infections are capable of inducing chronic inflammation, tissue necrosis or even life-threatening septicaemia. Infection of a device can thus transform a substantial health gain into a catastrophe. In addition to the devastating effect of these complications on the individual patients, the costs of the medical care of patients with infected devices are enormous. It has been estimated that the hospital care costs for the treatment of infected joint prostheses in the USA in 1988 was well over \$100 million. The scale of the morbidity and mortality together with the costs of treatment, thus provide a strong incentive to prevent these infections.

Perhaps the most common cause of device-related infections is related to catheter use, both urinary and intra-vascular. Studies in developed countries have indicated that the numbers of patients with these devices that develop infections is around 20% and 40%, respectively. Where septicemia ensues, the case-fatality ratio may be as high as 20 - 40%. Other specialised devices susceptible to infections include respiratory ventilators, haemodialysis units, cerebrospinal fluid shunts, cardiovascular implants, intra-ocular lenses, voice and auditory prostheses, restorative dental prostheses, breast implants and others. Some of these have a very low morbidity but high case - fatality ratio (eg. Prosthetic heart valve infection rate may be 1 - 2% but with 50 - 60% mortality). In other cases there may be economic losses because of the need to replace the device (eg. Voice prostheses due to microbial biofilm development and consequent material-degradation).

A wide variety of organisms are capable of initiating these iatrogenic infections. The proportions vary with the type of device and medical procedure, but include *Enterobacter* spp, *Enterococcus* spp, *Escherichia coli*, *Klebsiella* spp, *Pseudomonas aeruginosa*, *Staphylococcus* spp, *Candida albicans* and others. Often the organism may arise from the

patients own body flora but may also result from the hospital environment or nursing procedures.

Triclosan (generic name) is a well-known broad spectrum antimicrobial agent for topical applications in cosmetic applications and for general hygiene applications, such as the antimicrobial applications to inanimate substrates, such as textiles.

Triclosan (2,4,4'-trichloro-2'-hydroxy diphenyl ether) has the molecular formula $C_{12}H_7Cl_3O_2$ and is commercially available under the trade names Irgasan (Ciba-Geigy Limited) and Microban (Hoechst Celanese). Its physical properties, toxicology and compatibility with various chemicals used in the hygiene area are well documented. Its uses extend from additives to soaps, deodorants and toothpastes to incorporation in textile materials and yarns. It is incorporated into clothing to control the growth of microorganisms between launderings. Other common applications include animal beds, dental floss, shoe innersoles, furniture coverings and public transport seating, to name but a few.

In the medical field it is used in the material of hospital bed sheets, surgical drapes, hospital gowns, operating gowns, and medical masks. Potential medical applications include bandages, gauze, filters and anywhere a textile or textile fibre could be used to control mould, mildew, fungus, yeast or bacterial growth.

In recent previously unreported veterinary trials with woven bandages made from polymeric fibres incorporating Triclosan, the bandages exhibited a hitherto unexpected therapeutic, possibly synergistic, property, which essentially promotes better wound care management and wound healing. This in turn has led to the development of the present invention and the extension of the use of Triclosan - containing polymers in in-vivo applications of medical devices and prostheses for improved biocompatibility, infection control and wound care management following, for example, surgical procedures.

DISCLOSURE OF THE INVENTION

It is an object of the present invention to provide new or improved polymeric materials, and medical devices and prostheses comprising such polymeric materials, which go at least some way towards overcoming or at least minimising the prior art problems or limitations outlined above.

These and other objects of the invention will become more apparent from the following description.

According to one aspect of the present invention there is provided a biomaterial comprising an antimicrobial or therapeutically effective amount of Triclosan, when used in the manufacture of a medical device or prosthesis for internal or in vivo medical applications.

According to a further aspect of the invention there is provided medical devices or prostheses comprising the said biomaterial.

BEST MODE OF CARRYING OUT THE INVENTION

Triclosan is readily available commercially with a purity greater than 99%. The compound exhibits marked anti-microbial properties across a wide range of bacteria or fungi, including most of those mentioned above as being causative agents of iatrogenic infections. In its usage to date, Triclosan has not induced resistance in exposed organisms. The product has been marketed for many years as an anti-microbial system for preserving cosmetics and industrial products, for oral care products such as toothpaste and or hand disinfectants. Through these uses it has undergone extensive toxicological testing and been found to be safe at recommended concentrations. Additionally, the chemical has good environmental properties, yet is stable to hydrolysis. It is poorly soluble in water and highly soluble in many organic solvents.

The properties of Triclosan have not previously been considered to be therapeutic in nature. According to the present invention it is proposed that, by appropriate application,

the chemical can be used in therapeutic situations in conjunction with therapeutic devices and prostheses. According to the invention, various types of biomaterials, including ceramics and polymers, can be produced incorporating Triclosan that would have distinct advantages over currently available and used materials. This has the potential to provide significant socio-economic benefits to both individuals and communities through decreased likelihood of iatrogenic infections and consequent shorter periods of hospitalisation/treatment.

According to the invention, Triclosan is incorporated into the biomaterial by addition of Triclosan during the mixing/polymerisation stage, whereby the Triclosan is colloidally and homogeneously suspended within the amorphous zone of the polymer or other biomaterial. The Triclosan is introduced into the interstitial spaces of the polymer or other biomaterial in such a way as to not effect the physical properties of the biomaterial. These spaces act as reservoir for the Triclosan from which sub-micron sized particles thereof migrate to the surface of the biomaterial on demand. There they become a tightly bound durable part of the surface itself.

As the surface is cleaned or abraded during normal use, some of the surface layer may be removed. Instantly, the resulting imbalance in the internal vapour pressure begins pushing more active ingredient to the surface until equilibrium is re-established. This unique feature means that the surface of the biomaterial can be engineered to retain antimicrobial and biocompatible for the life of the product, and provides continuous, inherent control of the growth of broad range of microorganisms, including gram-positive and gram-negative bacteria, as well as fungi, moulds, mildew and yeasts. Triclosan is also believed to exhibit some virus-inactivating properties which prevent virus replication.

Triclosan penetrates and disrupts the metabolic function of thin-walled microorganisms, interrupting their ability to function, grow and reproduce. Normal human cells are thick-walled, and are therefore unaffected by Triclosan.

The antimicrobial biomaterials according to the present invention comprise a therapeutically effective amount of Triclosan. The amount used is for the most part arbitrary, depending primarily on the requirements of the particular application and the cost versus effective use life.

Preferably, Triclosan is incorporated into the polymer or other biomaterial in the range of from about 0.5% to about 5% by weight of the biomaterial, depending on the use requirements, but this range may be varied as required.

Generally, the present invention is applicable to any polymeric material or other biomaterial used in medical applications for the manufacture of medical devices or prostheses, including but not limited to polyvinyl chloride (PVC), polyamides, polystyrene, teflon as well as metals and ceramics. The antimicrobial polymeric material can be utilised in cast, extruded, injection moulded, rotary moulded or blow moulded products, or in products which are machined according to end use requirements. The invention is also applicable to durable coatings of biomaterials, such as polymeric coatings, applied to metallic surfaces, as may be required for some prostheses.

Although exemplary embodiments of the present invention have been referred to herein, it will be apparent to those having ordinary skill in the art that a number of changes, modifications or alternations to the invention described herein may be made, none of which depart from the spirit of the present invention. All such changes, modification, and alternations should therefore be seen as being within the scope of the present invention.

It should be appreciated that the present invention provides a substantial advance in antimicrobial biocompatible medical devices and prostheses providing all the herein-described advantages without incurring any relative disadvantages.

CLAIMS

1. A biomaterial comprising an antimicrobial or therapeutically effective amount of 2,4,4'-trichloro-2'-hydroxy diphenyl ether, when used in the manufacture of a medical device or prosthesis for in vivo medical applications.
2. A medical device or prosthesis for in vivo medical applications comprising a biomaterial containing an antimicrobial or therapeutically effective amount of 2,4,4'-trichloro-2'-hydroxy diphenyl ether.
3. A medical device or prosthesis according to claim 1 or claim 2 wherein the biomaterial is selected from synthetic polymers, metals and ceramics, or metal coated or sheathed with a synthetic polymer or ceramic.
4. A medical device or prosthesis according to claim 3, wherein the synthetic polymer is selected from polyvinyl chloride, polyamides, polystyrene and teflon.
5. A medical device or prosthesis according to any preceding claim, wherein the active ingredient is incorporated into the biomaterial in an amount of from about 0.5% to about 5.0% by weight of the biomaterial.

AMENDED CLAIMS

[received by the International Bureau on 13 February 1997 (13.02.97);
original claims 1-5 replaced by amended claims 1-4 (1 page)]

1. An implantable medical device or endoprosthesis for in vivo medical applications comprising a biomaterial containing an antimicrobial or therapeutically effective amount of 2,4,4¹-trichloro-2¹-hydroxy diphenyl ether.
2. An implantable medical device or endoprosthesis according to claim 1, wherein the biomaterial is selected from synthetic polymers, metals and ceramics, or metal coated or sheathed with a synthetic polymer or ceramic.
3. An implantable medical device or endoprosthesis according to claim 2, wherein the synthetic polymer is selected from polyvinyl chloride, polyamides, polystyrene and teflon.
4. An implantable medical device or endoprosthesis according to any preceding claim, wherein the active ingredient is incorporated into the biomaterial in an amount of from about 0.5% to about 5.0% by weight of the biomaterial.

STATEMENT UNDER ARTICLE 19

New claims 1 - 4 inclusive are based on originally filed claims 2 - 5, respectively. The new claims are especially directed towards implantable medical devices, including long-term or permanently implantable medical devices and endoprostheses, as distinct from short-term or percutaneous medical devices such as catheters. The inclusion of 2,4,4'-trichloro-2'-hydroxy diphenyl ether (Triclosan) in the matrix of the biomaterial of which the medical device or endoprosthesis is comprised promotes wound healing and inhibits or reduces bio-deterioration resulting from in vivo interaction between the biomaterial and microorganisms.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00642

A. CLASSIFICATION OF SUBJECT MATTER		
Int Cl ⁶ : A61L 27/00, 29/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC : A61L 17/00, 25/00, 27/00, 29/00, 31/00		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU : as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) DERWENT : TRICLOSAN		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96/22114 A (VITAPHORE CORPORATION) 25 July 1996 whole document	1-3, 5
X	WO 90/02573 A (SMITH & NEPHEW PLC) 22 March 1990 whole document	1-5
X	WO 90/01956 A (SMITH & NEPHEW PLC) 8 March 1990 whole document	1, 2, 3, 5
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 26 November 1996		Date of mailing of the international search report 4 Dec 1996
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929		Authorized officer GAYE HOROBIN Telephone No.: (06) 283 2069

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C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 33273/89 A (605419) (SMITH & NEPHEW PLC) whole document	1-5

INTERNATIONAL SEARCH REPORT

International Application No.

Information on patent family members

PCT/AU 96/00642

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
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WO	9002573	AT	102053	AT	130767	AU	41965/89
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		DE	68924981	EP	433332	EP	433358
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		GB	9023372	GB	2243835	JP	4500469
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		WO	9002573				
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